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Use of a multibotanical (Nutrafem) for the relief of menopausal vasomotor symptoms: a double-blind, placebo-controlled study

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Abstract

Objective: This study aimed to compare the efficacy and safety of a multibotanical (Nutrafem) with those of placebo for the treatment of menopausal vasomotor symptoms.

Methods: In this phase III, double-blind, randomized, placebo-controlled study, 159 postmenopausal women experiencing at least 21 vasomotor symptoms per week were treated with Nutrafem (Bionutra Pte Ltd, Singapore) or a matched placebo for 12 weeks. Treatment outcome was evaluated by the change from baseline in the average weekly number of vasomotor symptoms.

Results: At the end of the study, Nutrafem reduced the number of vasomotor symptoms by 46% from baseline, and this is significantly superior to placebo (26% from baseline; $P = 0.020$). Forty-three percent of women taking Nutrafem experienced an at least 50% reduction in the number of symptoms compared with 6% of women taking placebo ($P = 0.021$; number needed to treat = 2.7). There were no group differences in adverse events, laboratory values, and gynecological data.

Conclusions: Nutrafem is an effective botanical treatment for vasomotor symptoms in postmenopausal women.

Key Words: Menopause – Botanical – Hot flush – Night sweat – Vasomotor symptom – *Eucommia ulmoides* – *Vigna radiata*.

An estimated 47 million women worldwide enter menopause each year.[1] Of these, two of three experience menopausal symptoms, especially vasomotor symptoms such as hot flushes and night sweats.[2] These can be so severe that they affect quality of life and are usually the primary reason women seek medical attention for menopausal symptoms.[3]

There are many different options for managing menopause symptoms, including lifestyle modifications (lowering core body temperature by keeping cool and relaxation techniques),[4,5] hormone therapy (HT),[6] and natural remedies.[7] The results from the Women's Health Initiative[8] and follow-up from the Heart and Estrogen/Progestin Replacement Study[9,10] demonstrating an increased risk of cardiovascular disease and breast cancer among women on HT have reduced women's use of HT.[11,12] Many women are now choosing complementary and alternative medicines (CAMs) for the treatment of menopause-related problems.[13] The use of CAMs is further reinforced by the idea that they are natural and safe.[14,15]

One of these products is Nutrafem (Bionutra Pte Ltd, Singapore), a dietary supplement marketed for the management of symptoms associated with menopause. Nutrafem is a combination of botanical extracts derived from *Vigna radiata*, commonly known as mung beans, and *Eucommia ulmoides* bark. Initial in vitro studies have shown that Nutrafem activates liganded estrogen receptor systems without increasing breast cancer cell proliferation (manuscript in preparation). This shows that it has potential to be an effective and safe therapy for menopausal discomforts. Thus, the objective of this study was to investigate the efficacy and safety of Nutrafem compared with those of placebo for the treatment of vasomotor symptoms associated with menopause.

METHODS

This was a phase III, double-blind, randomized, placebo-controlled, multicenter clinical study. This study was designed, conducted, and reported in accordance with the International Conference on Harmonization of Technical Requirements (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (Declaration of Helsinki) and the relevant regulatory requirements in Singapore and the Philippines. The protocol was approved by the institutional review boards of each clinical site.

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The participants were recruited from gynecological clinics at hospitals in Singapore and the Philippines. All participants gave their written informed consent before enrollment. To keep participant information confidential, the participants were given a number code for identification. Prescreening of the participants was conducted by telephone. Eligibility for the study was limited to postmenopausal women who (1) were nonsmokers, (2) were 45 to 60 years old, (3) had a minimum of 1 year of spontaneous amenorrhea, and (4) experienced an average of at least 21 hot flushes or night sweats per week, including six or more of moderate or severe intensity for 2 weeks. Participants were excluded if they had received HT or oral contraceptives within the past 3 months or had used any CAM for menopausal symptoms within the past month. The participants were also instructed not to take any such treatments and were encouraged to notify their physicians before taking any medication during the study. In addition, women were excluded if they had (1) a history of any cancer, (2) a history of metabolic disorder, (3) allergic reactions to compounds similar to those in the investigational product, (4) participated in other clinical trials within the previous 30 days, or (5) had an abnormal mammogram result within 1 year and/or an abnormal Papanicolaou test result within 6 months of enrollment in the study.

Eligible participants were randomized into two groups in blocks of four.[16] One group received Nutrafem and the other received placebo. A 3:1 allocation was used, in which three women were assigned to the Nutrafem group for each woman assigned to the placebo group, to better assess the safety of Nutrafem. Nutrafem or placebo (in identical packaging) was supplied as a package of 20 blister packs, each containing 10 capsules. Each capsule of Nutrafem contains 75 mg of *E. ulmoides* plant extract and 150 mg of *V. radiata* plant extract, prepared according to Good Manufacturing Practice standards. Participants were instructed to take four capsules daily, two in the morning and two at night, for 12 consecutive weeks. Empty and unused packs were returned to the investigator.

Each study participant visited the clinics four times: for baseline screening, enrollment (week 0), and in weeks 6 and 12. The participants were asked to record the frequency and severity of hot flushes or night sweats every day and to judge the intensity of each vasomotor symptom by assigning it a score from 1 through 4 depending on whether it was mild, moderate, severe, or very severe. If a participant experienced no symptoms, the day was scored 0. The participants were taught to recognize their symptoms, evaluate the intensity of these symptoms, and make proper records on a daily-diary card. At weeks 0, 6, and 12, the diary cards were reviewed for numbers and intensity of vasomotor symptoms. At weeks 0 and 12, fasting blood was drawn for hematology and clinical chemistry assessments. Similarly, transvaginal ultrasound was performed on all participants to determine the endometrial thickness.

The primary efficacy parameter was changes in the reported frequency of vasomotor symptoms from the baseline to weeks 6 and 12 of treatment. The secondary efficacy parameter was the proportion of women achieving a 50% reduction from baseline in the number of vasomotor symptoms. Safety assessment was performed by monitoring the incidence of adverse events. Parameter changes were determined from physical examination, vital sign measurement, laboratory hematology and clinical chemistry tests, and gynecological information. All laboratory tests were carried out by an accredited pathology laboratory.

Efficacy analyses were performed on the intent-to-treat data sets. The intent-to-treat data sets were defined as all the participants who were randomized and had received at least one single dose of treatment and whose efficacy assessments were available at baseline and at least one follow-up visit. Safety analyses were performed on safety data sets. The safety data sets included all the participants who were randomized and had received at least one single dose of the treatment and whose safety assessments were available at the baseline and at least one follow-up visit. In the event of missing values, the last-observation-carried-forward technique was used for the final assessment of efficacy. For those women who prematurely discontinued the study, the last assessments obtained were carried forward to all subsequent visits.

The average number of vasomotor symptoms and average severity score were calculated for each week. The average weekly vasomotor symptom severity score was calculated as follows: ([number of mild vasomotor symptoms $\times$ 1] + [number of moderate vasomotor symptoms $\times$ 2] + [number of severe vasomotor symptoms $\times$ 3] + [number of very severe vasomotor symptoms $\times$ 4])/total number of vasomotor symptoms. The change from baseline to each week was summarized and analyzed by the paired *t* test within each arm and two-sample *t* tests between the two arms. The vasomotor symptom changes were also analyzed using analysis of covariance (ANCOVA) with adjustments for baseline frequency or severity. The proportion of participants with an at least 50% reduction in the number of hot flushes was analyzed by conditional logistic regression with treatment and study site as covariates. The number and percentage of participants experiencing adverse events were tabulated by the primary system organ class according to the MedDRA classification system. Data analysis was performed using Stata version 10.1 (Stata Corporation, College Station, TX).

All statistical tests were two sided and conducted at the 5% level of significance. The null hypothesis was that the two treatments were equally effective and safe. *P* values were reported to three decimal places, and 95% CIs were constructed as required.

RESULTS

A total of 215 women were screened, and 159 were randomly assigned to receive either Nutrafem or placebo (Fig. 1). Of these 159 women, 131 (82%) completed the baseline evaluation and at least one other visit for efficacy endpoints, and 111 (85%) of 131 women completed the

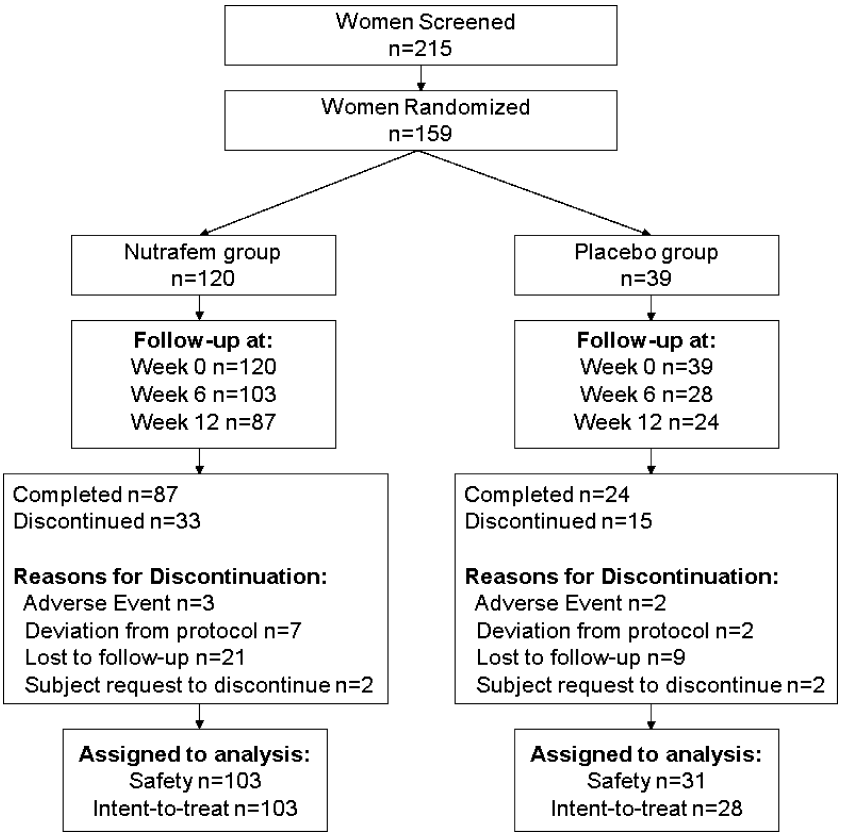

FIG. 1. Participant population data sets.

entire study. There was no significant difference between the Nutrafem and placebo groups in the percentage of dropouts (P = 0.195). Based on returned pill counts, treatment dose compliance was 80% in the Nutrafem group and 74% in the placebo group, with no significant difference between the two groups (P = 0.311).

Participant demographics and baseline values for the frequency and severity of vasomotor symptoms were not significantly different between treatment groups (Table 1). Participants' mean age was 54.4 years (range, 47-61 y), and the mean number of years since natural menopause was 5.1 years (range, 1-17 y). At baseline, the mean weekly number of vasomotor symptoms was 24.8 and the mean weekly vasomotor symptom score was 48.7.

The decrease from baseline in the average weekly number of vasomotor symptoms over the study is shown for each group in Fig. 2. The participants in the Nutrafem group experienced a sharper decline in the number of hot flushes or night sweats than did those in the placebo group. At the end of the study, the number of vasomotor symptoms decreased by 46% in the treatment group and 26% in the placebo group.

Treatment with Nutrafem produced a significantly greater decrease from baseline in the average weekly number of vasomotor symptoms compared with placebo at both week

TABLE 1. *Demographics and baseline clinical characteristics*

	Nutrafem (n = 103)	Placebo (n = 28)	*P*
Demographics			
Age, y			0.649
Mean (SD)	54.3 (3.3)	54.7 (4.6)	
Range	47-61	47-61	
Height, cm	155.63 (5.43)	154.23 (5.82)	0.234
Body weight, kg	56.04 (9.51)	54.02 (9.95)	0.327
Body mass index, kg/m^2	23.17 (3.69)	22.89 (3.95)	0.708
Menstruation history, y			
Age at menarche	13.3 (1.8)	13.3 (1.7)	0.854
Age at menopause	49.3 (3.1)	48.8 (4.0)	0.427
Years since menopause	4.9 (3.4)	5.8 (3.9)	0.214
Baseline efficacy characteristics			
Weekly number of vasomotor symptoms	25.43 (10.22)	22.61 (7.13)	0.098
Weekly vasomotor symptom severity score	49.21 (31.87)	46.59 (20.31)	0.599

Values are presented as mean (SD) unless otherwise specified.

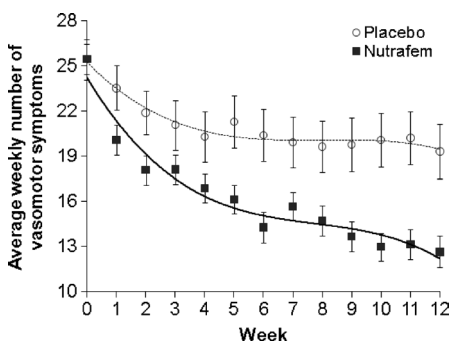

FIG. 2. Vasomotor symptom frequency adjusted for baseline. Error bars indicate SE. Mean reduction from baseline is statistically different from placebo (P < 0.05) beyond week 4.

TABLE 2. *Summary of efficacy results at weeks 6 and 12*

	Week 6			Week 12		
	Nutrafem (n = 103)	Placebo (n = 28)	*P*	Nutrafem (n = 103)	Placebo (n = 28)	*P*
Number of vasomotor symptoms						
Absolute reduction	11.17 (12.17)	5.04 (7.33)	0.001	12.80 (13.87)	6.11 (7.29)	0.001
Percentage reduction	41.64 (40.84)	21.53 (36.35)	0.020	46.31 (41.78)	25.78 (36.55)	0.020
Vasomotor symptom severity score						
Absolute reduction	24.22 (31.95)	12.59 (16.85)	0.011	26.52 (36.05)	15.13 (17.55)	0.021
Percentage reduction	44.44 (45.57)	25.12 (43.81)	0.047	47.97 (47.32)	29.65 (44.09)	0.068

Values are presented as mean (SD).

6 (−11.17 compared with −5.04 hot flushes, respectively; $P = 0.001$) and week 12 (−12.80 compared with −6.11 hot flushes, respectively; $P = 0.001$; Table 2). After adjustment of the baseline number of vasomotor symptoms, the ANCOVA showed that the reduction in weekly average number of hot flushes between the two groups was significantly different ($P = 0.037$ for week 6; $P = 0.046$ for week 12).

The vasomotor symptom–weighted severity score decreased by 27 points in the Nutrafem group and 15 points in the placebo group at week 12. The reductions from baseline between the two groups were significantly different ($P = 0.021$). However, the ANCOVA after adjustment of the baseline severity showed that the differences in reductions between the two groups were only nearly significant ($P = 0.073$), perhaps because of the high variation in scores.

Figure 3 shows the proportion of women with an at least 50% decrease from baseline in the average weekly number of vasomotor symptoms at weeks 6 and 12. At weeks 6 and 12, significantly more women taking Nutrafem achieved an at least 50% reduction compared with women taking placebo ($P = 0.042$ and $P = 0.021$, respectively). Based on the 50% responder rates, the number needed to treat for benefit was 2.7 (95% CI, 1.9-4.5). This means that 1 in every 3 women will benefit from Nutrafem.

For the safety profile of Nutrafem or placebo, we evaluated 134 participants. Adverse events were experienced in 42% of the Nutrafem participants and 29% of the placebo participants. However, this was not significantly different (95% CI, −7.0% to 28.9%; $P = 0.2167$; Table 3). Most of the adverse events reported were mild (Nutrafem, 89.9%; placebo, 91.2%), not related to treatment (Nutrafem, 97.2%; placebo, 94.1%), and resolved (Nutrafem, 92.7%; placebo, 94.1%) with no action taken (Nutrafem, 98.2%; placebo, 97.1%). Only two participants from the Nutrafem group and one participant from the placebo group had the investigational drug dose interrupted, but this was within the dose compliance intake for the entire study. One severe adverse event (dengue fever) was reported in the Nutrafem group, but therapy was continued according to the study protocol.

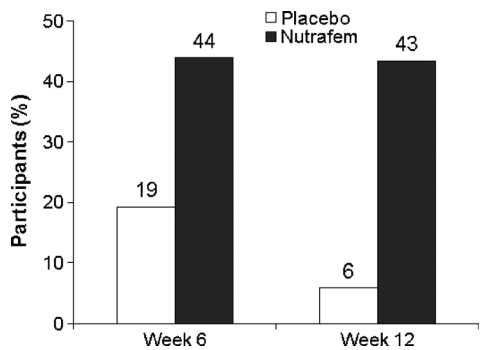

FIG. 3. Fifty percent responder rates. Percentage of women in the Nutrafem and placebo groups achieving an at least 50% reduction in the number of vasomotor symptoms at weeks 6 and 12. $P < 0.05$ compared with placebo.

According to system organ classification, the respiratory, thoracic, and mediastinal systems were the predominant adverse event groups (Nutrafem, 17.5%; placebo, 12.9%), followed by musculoskeletal and connective tissue disorders (Nutrafem, 9.7%; placebo, 12.9%). Two participants with hypersensitivity symptoms (immune system disorders classification) in the Nutrafem group were not withdrawn from the study because the symptoms were deemed mild and not related to the investigational product.

There were no significant differences in the change in physical examination, vital signs, hematology parameters, and gynecological examinations between the Nutrafem and placebo groups. Two participants with baseline hypercholesterolemia in the Nutrafem group were reported to have their total cholesterol status changed from nonclinically significant to clinically significant (from 5.38 to 6.04 mmol/L and from 5.71 to 6.40 mmol/L). The increase in blood cholesterol levels in these two participants was reported as adverse events that were not related to the study drug. There were no other clinically significant changes in liver function enzymes (aspartate aminotransferase and alanine aminotransferase) and other clinical chemistry parameters during the study period. There were also no abnormal findings or significant change in the endometrial thickness for both the Nutrafem and placebo groups ($P = 0.332$).

DISCUSSION

Most women experience unpleasant menopausal symptoms, especially vasomotor symptoms: hot flushes and night sweats. HT has been used for decades to relieve these symptoms. Although HT effectively combats these symptoms, in the last few years, several studies have suggested that HT may not be safe.[8-10,17-19] For some women, even using HT for less than 2 years can increase the risk of coronary heart disease, stroke, and venous thromboembolic disease.[20] Recently, researchers have treated hot flushes with

TABLE 3. *Adverse events by system organ class*

	Nutrafem (n = 103)			Placebo (n = 31)		
	n	%	e	n	%	e
Any symptom	43	41.7	109	9	29.0	34
Primary system organ class term						
Respiratory, thoracic, and mediastinal disorders	18	17.5	25	4	12.9	11
Musculoskeletal and connective tissue disorders	10	9.7	21	4	12.9	5
Nervous system disorders	13	12.6	27	3	9.7	6
Skin and subcutaneous tissue disorders	2	1.9	2	3	9.7	3
Gastrointestinal disorders	10	9.7	15	2	6.4	2
General disorders and administration site conditions	6	5.8	7	2	6.4	4
Infections and infestations	2	1.9	2	1	3.2	1
Surgical and medical procedures	2	1.9	2	1	3.2	1
Reproductive system and breast disorders	1	0.9	1	1	3.2	1
Investigations	3	2.9	3	–	–	–
Immune system disorders	2	1.9	2	–	–	–
Ear and labyrinth disorders	1	0.9	1	–	–	–
Psychiatric disorders	1	0.9	1	–	–	–

n, number of women with adverse event; %, proportion of women in the study population having the adverse event; e, number of adverse events.

low-dose antidepressants, for example, selective serotonin reuptake inhibitors.[21,22] These are, however, not as effective as HT, and increasing the dose increases the number of adverse events.[23]

These discouraging studies have led an increasing number of women to use CAM, including herbal medicine. The botanicals most commonly used in menopause are soy, black cohosh, and red clover. Soy isoflavone extracts have had mixed effects on hot flushes in placebo-controlled trials,[24] possibly because of individual metabolic differences in the production of equol.[25] Black cohosh has shown some efficacy in reducing menopausal symptoms,[26-28] but there are safety concerns, especially about potential liver toxicity.[29,30] Furthermore, recent placebo-controlled studies have failed to provide evidence on the superiority of black cohosh over placebo in reducing vasomotor symptoms.[31,32] Red-clover isoflavones do not seem to lessen the frequency or severity of hot flushes in placebo-controlled trials.[24,33-37]

Nutrafem is a combination of two botanicals, *V. radiata* bean and *E. ulmoides* bark, both with a long history as food or herbal medicine. *V. radiata* has been consumed as a good source of essential fatty acids, antioxidants, minerals, and protein.[38] Other than its nutritional value, the bean has been used to reduce the adverse effects of breast cancer radiotherapy, such as headache, fatigue, sleeplessness, and weight loss.[39] *E. ulmoides* extract, rich in polyphenolic compounds such as lignans, phenolic acid, and flavonoids,[40] has antihypertensive,[41] antioxidant[42,43] and anti-inflammatory properties.[44] It also promotes collagen synthesis and has been suggested to treat postmenopausal osteoporosis.[45,46]

CONCLUSIONS

Initial findings using the estrogen reporter gene assay have shown that Nutrafem does not activate the estrogen receptor. However, in the presence of the receptors' cognate ligand, estradiol, the estrogen receptor transactivation increases with increasing Nutrafem exposure. Furthermore, in another in vitro assay, Nutrafem demonstrated antiproliferative action on human breast cancer cell lines (manuscript in preparation). In this randomized, placebo-controlled study, we investigated the efficacy of Nutrafem for the treatment of menopausal vasomotor complaints. Compared with placebo, Nutrafem significantly reduced the number and severity of hot flushes and night sweats in postmenopausal women, some of whom experienced a sharp reduction in the symptoms within 1 week of treatment. At the end of the study, the number of vasomotor symptoms was halved in 43% of women receiving Nutrafem, compared with 6% in the placebo group. Safety data suggest that Nutrafem was generally well tolerated, with no significant difference in adverse effects between the Nutrafem and placebo groups. This study indicates that Nutrafem is effective, safe, and well tolerated as a therapy for vasomotor symptoms of menopause.

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